



US005236941A

**United States Patent** [19]

Zask et al.

[11] **Patent Number:** 5,236,941[45] **Date of Patent:** Aug. 17, 1993

[54] **5-(2-HYDROXY-1-ARYLETHYLIDENE)- AND  
5-(2-OXO-1-ARYLETHYLIDENE)-2,4-  
THIAZOLIDINEDIONES AND  
DERIVATIVES THEREOF**

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[21] **Appl. No.:** 906,331

[22] **Filed:** Jun. 30, 1992

[51] **Int. Cl.<sup>3</sup>** ..... C07D 277/34; A61K 31/425

[52] **U.S. Cl.** ..... 514/369; 548/183

[58] **Field of Search** ..... 548/183; 514/369

[56] - **References Cited**

**U.S. PATENT DOCUMENTS**

4,738,972	4/1988	Eggler et al.	514/314
4,997,948	3/1991	Zask et al.	548/183
5,061,717	10/1991	Clark et al.	514/342
5,068,342	11/1991	Zask et al.	548/183
5,116,855	5/1992	Inoue	514/369
5,120,754	6/1992	Clark et al.	415/369

**FOREIGN PATENT DOCUMENTS**

0177353 10/1985 European Pat. Off. .

0332331 2/1989 European Pat. Off. .

**OTHER PUBLICATIONS**

Omar et al., Bull. Chem. Soc. Jpn., 64, 750-52 (1991).

Salama et al., Alex. J. Pharm. Sci. 4(1), 44-46 (1990).

Zask et al., J. Med. Chem. 33, 1418-23 (1990).

Yoshioka, et al., J. Med. Chem. 32, 421-28 (1989).

Fujita, et al., Diabetes 32, 804-810 (1983).

*Primary Examiner*—Robert Gerstl*Attorney, Agent, or Firm*—R. F. Boswell, Jr.[57] **ABSTRACT**

5-(2-Hydroxy-1-phenyl (or 1-naphthalenyl)ethylidene) and 5-(2-oxo-1-phenyl (or 1-naphthalenyl)ethylidene)-2,4-thiazolidinediones and derivatives thereof are useful in lowering blood glucose levels in a hyperglycemic laboratory animal model and are thus useful in the treatment of diabetes mellitus.

**14 Claims, No Drawings**



# 5-(2-HYDROXY-1-ARYLETHYLIDENE)- AND 5-(2-OXO-1-ARYLETHYLIDENE)-2,4-THIAZOLIDINEDIONES AND DERIVATIVES THEREOF

## FIELD OF INVENTION

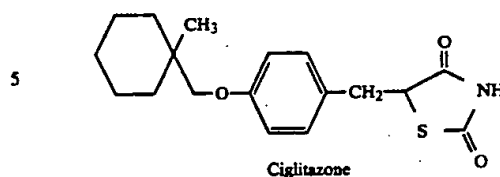
This invention relates to novel 5-(2-hydroxy-1-arylethylidene) and 5-(2-oxo-1-arylethylidene)-2,4-thiazolidinedione derivatives and pharmaceutically acceptable cationic salts thereof, a process for their preparation, and to their blood glucose lowering actions and their use in the treatment of diabetes mellitus.

## BACKGROUND OF THE INVENTION

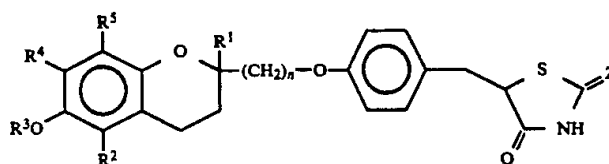
Diabetes mellitus is a syndrome characterized by

abnormal insulin production, increased urinary output and elevated blood glucose levels. There are two major subclasses of diabetes mellitus. One is the insulin-dependent diabetes mellitus (IDDM or Type I), formerly referred to as juvenile onset diabetes since it was evident early in life, and non-insulin dependent diabetes mellitus (NIDDM or Type II), often referred to as maturity-onset diabetes. Exogenous insulin by injection is used clinically to control diabetes but suffers from several drawbacks. Insulin is a protein and thus cannot be taken orally due to digestion and degradation but must be injected. It is not always possible to attain good control of blood sugar levels by insulin administration. Insulin resistance sometimes occurs requiring much higher doses of insulin than normal. Another shortcoming of insulin is that while it may control hormonal abnormalities, it does not always prevent the occurrence of complications such as neuropathy, retinopathy, glomerulosclerosis, or cardiovascular disorders.

Orally effective antihyperglycemic agents are used to reduce blood glucose levels and to reduce damage to the nervous, retinal, renal or vascular systems through mechanisms affecting glucose metabolism. Such agents act in a variety of different mechanisms including inhibition of fatty acid oxidation,  $\alpha$ -glycosidase inhibition, antagonism of  $\alpha_2$ -receptors and inhibition of gluconeogenesis. Two classes of compounds have predominated: the biguanides as represented by phenformin and the sulfonylureas as represented by tolbutamide (Orinase®). A third class of compounds which has shown antihyperglycemic activity are thiazolidinediones of which ciglitazone is the prototype. Ciglitazone suppresses the symptoms of diabetes-hyperglycemia, hypertriglyceridemia and hyperinsulinemia [Diabetes 32, 804-10 (1983)].



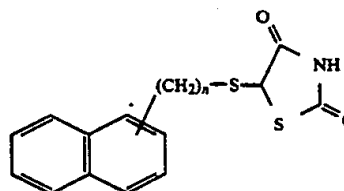
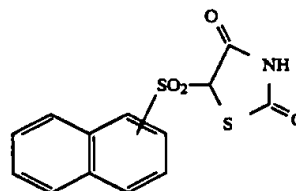
Yoshioka et al., J. Med. Chem. 32, 421-428 (1989) describe compounds where elements of Vitamin E, a potent antioxidant, and ciglitazone are combined that are useful for treating angiopathy (hyperlipidemia, diabetes and/or diabetic complications). These compounds have the formula:



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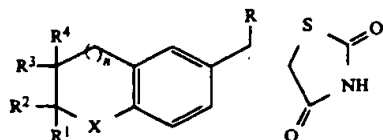
where R<sup>3</sup> is H, acyl or aroyl; R<sup>1</sup> and R<sup>2</sup> are H or lower alkyl, R<sup>4</sup> is H, lower alkyl or lower alkoxy; R<sup>5</sup> is lower alkyl or alkoxy, n is 1 or 2 and Z is O or NH.

Antihyperglycemic thiazolidinediones disclosed in our U.S. Pat. Nos. 4,997,948 and 5,068,342 and J. Med. Chem. 33(5), 1418-23 (1990) are represented by the following basic formulas:



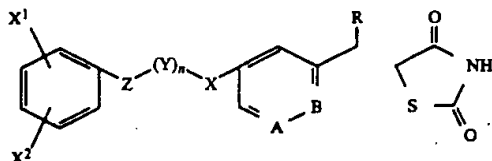
The synthesis of 5-(benzoylmethylidene)-2,4-thiazolidinediones via a 2-thioxo-4-thiazolidinone intermediate is reported in Bull. Chem. Soc. Jpn. 64(2), 750-752 (1991). The synthesis and in vitro antimicrobial evaluation of 5-(benzoylmethylidene)-2,4-thiazolidinediones and 3-(benzoylmethyl-5-benzoylmethylidene)-2,4-thiazolidinediones is described in Alex. J. Pharm. Sci., 4(1), 44-46 (1990). U.S. Pat. No. 4,738,972 discloses hypoglycemic thiazolidinediones of the formula:



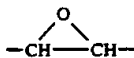


where X is  $-\text{CH}_2-$ ,  $-\text{CO}-$ ,  $-\text{CHOH}-$ , or  $-\text{NR}^5-$  and R is H, methyl or ethyl.

The European patent application 0332331A2 discloses hypoglycemic thiazolidine-2,4-diones which have the formula:



where either A or B is N and the other is  $-\text{CH}-$ , X is  $-\text{S}-$ ,  $-\text{SO}-$ ,  $-\text{SO}_2-$ ,  $-\text{CH}_2-$ ,  $-\text{CHOH}-$ , or  $-\text{CO}-$ ; n is 0 or 1, Y is  $\text{CHR}^1$  or  $\text{NR}^2$  and Z is  $-\text{CH}-$ ,  $-\text{R}^3-$ ,  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$ ,



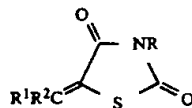
$-\text{OCH}_2-$ ,  $-\text{SCH}_2-$ ,  $-\text{SOCH}_2-$ , or  $-\text{SO}_2\text{CH}_2-$ ; and R, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are H or methyl. The dotted line in the above formula represents an optional bond.

The European Patent Application 0 177353A discloses 5-(4-substituted benzylidene)-2,4-thiazolidinediones which have blood glucose and lipid lowering activity useful for treating hyperlipidemia and diabetes.

Compounds of the present invention may thus be useful in the prevention and/or treatment of diabetic complications and as antihyperlipidemia and antihyperinsulinemic agents.

### SUMMARY OF THE INVENTION

The compounds of this invention which are useful in the treatment of diabetes mellitus through their blood glucose lowering actions have the structure of general formula I



wherein:

- R is H or lower alkyl,
- R<sup>1</sup> is phenyl, 2,3-dichlorophenyl, 1-naphthalenyl or 5-methyl-1-naphthalenyl;
- R<sup>2</sup> is R<sup>3</sup>-X- where X is  $-\text{CO}-$  or  $-\text{CHOR}^4-$  and when X is  $-\text{CHOR}^4-$ , R<sup>3</sup> is H, loweralkyl, or aryl where aryl is phenyl or naphthalenyl optionally substituted by halogen, lower alkyl or lower alkoxy and when X is  $-\text{CO}-$ , R<sup>3</sup> is H;
- R<sup>4</sup> is H or methyl;
- or a solvate or a pharmaceutically acceptable cationic salt thereof;

and R<sup>1</sup> and R<sup>2</sup> may be in the E or Z configuration with respect to the 2,4-thiazolidinedione ring.

Under the definitions of terms in Formula I, lower alkyl is C<sub>1</sub>-C<sub>6</sub> alkyl (straight and branched chain), lower alkoxy is -O-lower alkyl, and halogen is selected from fluorine, chlorine, bromine or iodine. The free valence of naphthalenyl is at either position 1 or 2.

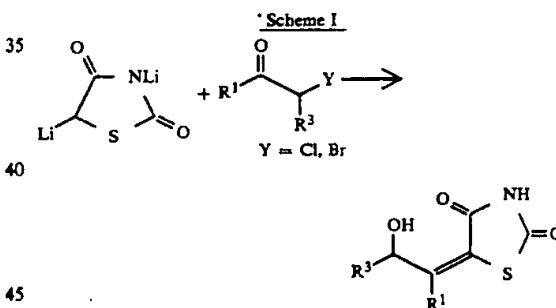
The preferred compounds of this invention are those where R is H or methyl and R<sup>3</sup> is H, methyl, or phenyl.

The blood glucose lowering activity of the compounds of formulas I of this invention were demonstrated in experiments using diabetic (db/db) mice. The db/db (C57BL/KsJ) mouse exhibits many metabolic abnormalities that are associated with non-insulin dependent diabetes mellitus (Type II) in humans. The animals are obese, glucose intolerant and have fasting hyperglycemia which is sometimes accompanied by a paradoxical hyperinsulinemia.

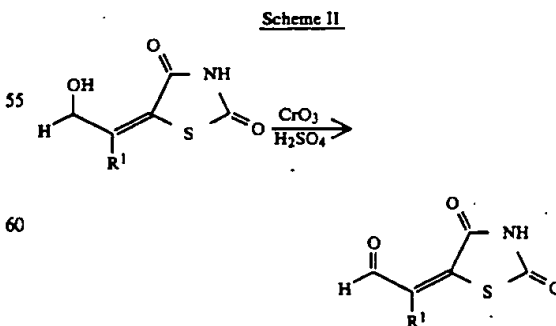
### DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are prepared by reaction of dilithio-2,4-thiazolidinedione (J. Med. Chem. 33, 1418 (1990), U.S. Pat. Nos. 4,997,948 and 5,068,342) with an  $\alpha$ -haloketone where R<sup>1</sup> and R<sup>3</sup> are as previously defined is reacted with an appropriate  $\alpha$ -haloketone as shown in Scheme I.

Only one of the two possible configurations is represented in Schemes I-V. Under Scheme I, when R<sup>3</sup> is H only the E isomer is observed. When R<sup>3</sup> is other than H, a mixture of E and Z isomers is observed.



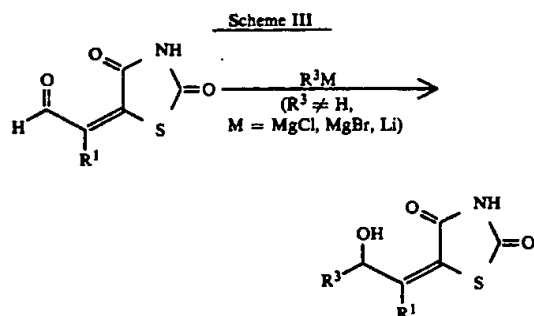
The Formula I aldehydes (X =  $-\text{CO}-$ , R<sup>3</sup> = H) are obtained by oxidation of the corresponding alcohol (Scheme II) using Jones reagent.



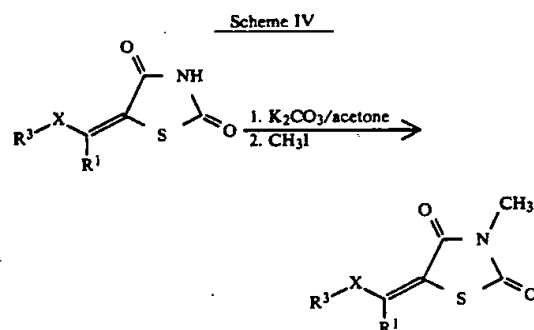
As an alternative procedure to Scheme I, Formula I compounds where R<sup>3</sup> is lower alkyl or aryl can be obtained by reaction of the aldehyde obtained in Scheme



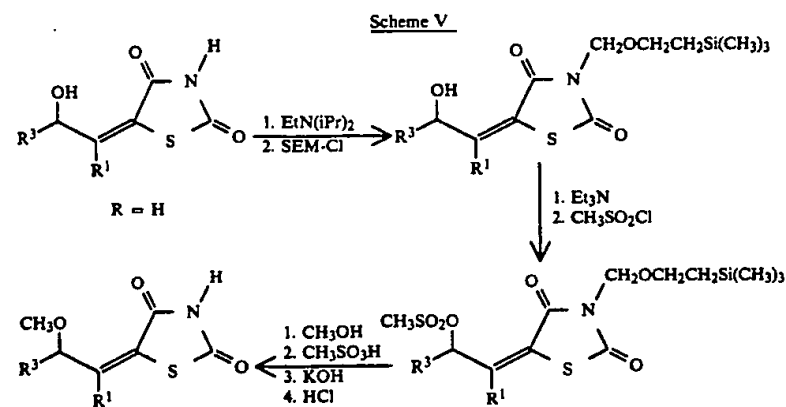
II with an appropriate Grignard or lithium reagent as shown in Scheme III.



Formula I compounds where R is lower alkyl, illustratively methyl, can be prepared as outlined in Scheme IV.



Formula I compounds where R<sup>4</sup> is methyl can be prepared according to the steps outlined in Scheme V. Where R is H, protection of the nitrogen atom at position 3 is required with a protecting group such as trimethylsilylethoxymethyl which can be readily removed.



## SALTS

The compounds of formula I form cationic salts with suitable therapeutically acceptable inorganic and organic bases. These derived salts possess the same activity as their parent acid and are included within the scope of this invention. Suitable inorganic bases to form these salts include, for example, the hydroxides, carbonates or bicarbonates of the therapeutically acceptable alkali

metals or alkaline earth metals such as sodium, potassium, magnesium, calcium and the like. Suitable organic bases include amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol), procaine, etc. Furthermore, there may be mentioned the quaternary salts, for example, the tetraalkyl (e.g. tetramethyl), alkyl-alkanol (e.g. methyltriethanol) and cyclic (e.g. N,N-dimethylmorpholine) ammonium salts. In principle, however, there can be used all the ammonium salts which are physiologically compatible.

Transformations to the corresponding salts are readily carried out by reacting the acid form of the compounds of formula I with an appropriate base, usually one equivalent, in a co-solvent. The salt is isolated by concentration to dryness or by adding of a non-solvent. For example, in the case of inorganic salts, it is preferred to dissolve the acid of Formula I in water containing a hydroxide, carbonate or bicarbonate corresponding to the inorganic salt desired. Evaporation of the solution or addition of a water-miscible solvent of more moderate polarity, for example, a lower alkanol such as butanol, or a lower alkanone such as ethyl methyl ketone, gives the solid inorganic salt. In the case of an amine salt, it is preferred to use a cosolvent of moderate or low polarity such as ethanol, ethyl acetate and benzene. Evaporation of the solvent or addition of a miscible diluent of lower polarity such as benzene or n-hexane gives the solid salt. Quaternary ammonium salts may be prepared by mixing the acid of formula I with a quaternary ammonium hydroxide in water solution followed by evaporation of the water.

The following specific examples are included for illustrative purposes and should not be considered as limiting the scope of this disclosure in any way. All starting materials are either commercially available or can be prepared by standard procedures known to one skilled in the art.

## EXAMPLE 1

### 5-[2-Hydroxy-1-(1-naphthalenyl)ethylidene]-2,4-thiazolidinedione

To a solution of 2,4-thiazolidinedione (1.47 g, 12.6 mmol) in tetrahydrofuran (75 ml) at  $-78^\circ\text{C}$ . was added n-butyllithium (17.3 mL, 27.6 mmol, 1.6M). The result-



ing white heterogeneous mixture was stirred at 78° C. for 1 h then treated with a solution of 2-bromo-1-(naphthalen-1-yl)ethanone (3.12 g, 12.6 mmol) in tetrahydrofuran (35 mL). After 1 h at -78° C., the reaction mixture was allowed to warm to 25° C. After 2 h excess solid ammonium chloride was added. The mixture was then partitioned between 5% aqueous sulfuric acid and chloroform. The aqueous phase was washed an additional two times with chloroform and the organic phases were then combined and dried over magnesium sulfate. Concentration in vacuo gave an orange oil (4.66 g). Flash chromatography (300 g silica gel, pretreated with 2% H<sub>3</sub>PO<sub>4</sub>/methanol; chloroform) gave the E-isomer of the title compound as a yellow oil (2.15 g) which was further purified by reverse phase chromatography (25 g C<sub>18</sub> silica gel, methanol/brine). Crystals (1.82 g, 51%) were obtained which were recrystallized from methanol/H<sub>2</sub>O to give the analytically pure product (1.2 g).

m.p. 169°-170° C.

IR (KBr): 3460 (bd), 3130 (m), 3030 (bd), 1733 (s), 1700 (s), 1325 (s), 1170 (m), 775 (s) cm<sup>-1</sup>.

MS (EI) m/e (relative intensity): 285 (M<sup>+</sup>, 50), 256 (25), 242 (5), 196 (33), 155 (29), 153 (56), 152 (100), 128 (55), 127 (13).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz): δ 5.02 (s, 2H, -CH<sub>2</sub>-), 7.34-8.01 (m, 7H, ArH) Analysis calculated (C<sub>15</sub>H<sub>11</sub>NO<sub>3</sub>S): C, 63.15; H, 3.86; N, 4.91. Found: C, 62.77; H, 4.12; N, 4.80.

#### EXAMPLE 2

##### 5-[2-Hydroxy-1-(5-methylnaphthalen-1-yl)ethylidene]-2,4-thiazolidinedione.

Following the procedure of Example 1, the E-isomer of the title compound was prepared from 2,4-thiazolidinedione and 2-bromo-1-(5-methylnaphthalen-1-yl)ethanone.

m.p. 160°-161° C.

IR (KBr): 3435 (bd), 1731 (s), 1685 (s), 1608 (m), 1324 (s), 781 (s) cm<sup>-1</sup>.

MS (EI) m/e (relative intensity): 299 (M<sup>+</sup>, 96), 270 (30), 210 (100), 197 (37), 165 (63), 152 (50).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.75 (s, 3H, CH<sub>3</sub>), 4.21 (dd, J=6.9, 8.6 Hz, 1H, -OH), 4.77 (dd, J=8.7, 14.7 Hz, 1H, -CHH-), 4.88 (dd, J=6.8, 14.7 Hz, 1H, -CHH-), 7.35-8.15 (m, 6H, ArH).

Analysis Calculated (C<sub>16</sub>H<sub>13</sub>NO<sub>3</sub>S): C, 64.17; H, 4.34; N, 4.68. Found: C, 63.41; H, 4.49; N, 4.54.

#### EXAMPLE 3

##### 5-[2-Oxo-1-(1-naphthalenyl)ethylidene]-2,4-thiazolidinedione

To a solution of 5-[2-hydroxy-1-(1-naphthalenyl)ethylidene]-2,4-thiazolidinedione (10.13 g, 35.5 mmol) in acetone (250 mL) at 0° C. was added Jones reagent (8N, 10.26 mL, 82 mmol). After 30 min 2-propanol (10 mL) was added. The reaction mixture was filtered and concentrated in vacuo. The resulting oil was taken up in ether and washed with water (2×). The organic phase was dried over magnesium sulfate, filtered and concentrated to give a foam (9.88 g). Recrystallization (chloroform/ethyl acetate) gave crystals (6.87 g) of the E-isomer. m.p. 184°-185° C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.36-8.04 (m, 7H, ArH), 10.9 (s, 1H, CHO).

Analysis Calculated (C<sub>15</sub>H<sub>9</sub>NO<sub>3</sub>S): C, 63.59; H, 3.20; N, 4.94. Found: C, 63.32; H, 2.98; N, 4.92.

#### EXAMPLE 4

##### 5-[2-Hydroxy-1,2-diphenylethylidene]-2,4-thiazolidinedione

5-(2-Hydroxy-1-phenylethylidene)-2,4-thiazolidinedione was prepared by the procedure of Example 1 from 2,4-thiazolidinedione and 2-bromoacetophenone.

M.P. 175°-176° C.

IR (KBr): 3370 (bd s), 1733 (s), 1690 (s), 1609 (s), 1329 (s), 1184 (s), 830 (m), 815 (m) cm<sup>-1</sup>.

MS (EI) m/e (relative intensity): 235 (M<sup>+</sup>, 43), 206 (100), 192 (9), 135 (48), 134 (74).

<sup>1</sup>H NMR (acetonitrile-d<sub>3</sub>): δ 4.92 (s, -CH<sub>2</sub>OH, 2H), 7.32-7.54 (m, ArH, 5H).

Analysis Calculated (C<sub>11</sub>H<sub>9</sub>NO<sub>3</sub>S): C, 56.16; H, 3.86; N, 5.95. Found: C, 56.20; H, 3.91; N, 6.00.

5-(2-Hydroxy-1-phenylethylidene)-2,4-thiazolidinedione was converted to 5-(2-oxo-1-phenylethylidene)-2,4-thiazolidinedione by the procedure of Example 3. m.p. 168°-169° C.

MS (EI) m/e (relative intensity): 233 (M<sup>+</sup>, 13), 205 (14), 134 (100).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 7.2-7.5 (m, 5H, ArH), 10.7 (s, 1H, -CHO).

Analysis Calculated (C<sub>11</sub>H<sub>7</sub>NO<sub>3</sub>S): C, 56.64; H, 3.02; N, 6.00. Found: C, 56.64; H, 3.19; N, 6.27.

To a solution of 5-(2-oxo-1-phenylethylidene)-2,4-thiazolidinedione in tetrahydrofuran (50 mL) at -78° C. was added phenylmagnesium chloride (11.7 mL, 2M, 23.4 mmol) dropwise over 5 min. After 5 min the reaction mixture was allowed to warm to 25° C. The reaction mixture was partitioned between 2N HCl and ether. The organic layer was dried over magnesium sulfate and concentrated to an oil. Chromatography (silica gel) followed by recrystallization (hexane/ether) gave the E-isomer as a white powder (10 g).

m.p. 96°-98° C.

IR (KBr): 3430 (bd), 1739 (s), 1682 (s), 1610 (w), 1600 (w), 1171 (m), 702 (s) cm<sup>-1</sup>.

MS (EI) m/e (relative intensity): 311 (M<sup>+</sup>, 26), 206 (100), 135 (21), 134 (32), 105 (73).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 6.04 (d, J=3.6 Hz, 1H, -CH-), 6.87 (d, J=7 Hz, 2H, ArH), 7.16-7.36 (m, 8H, ArH), 12.5 (bd s, 1H, -NH).

Analysis Calculated (C<sub>17</sub>H<sub>13</sub>NO<sub>3</sub>S.H<sub>2</sub>O): C, 61.99; H, 4.59; N, 4.25. Found: C, 63.30; H, 4.71; N, 4.25.

#### EXAMPLE 5

##### 5-[2-Hydroxy-1-(3,4-dichlorophenyl)ethylidene]-2,4-thiazolidinedione

The E-isomer of the title compound was prepared according to the procedure of Example 1 from 2,4-thiazolidinedione and 2,3',4'-trichloroacetophenone.

m.p. 186°-187° C.

IR (KBr): 3466 (bd), 1727 (s), 1701 (s), 1585 (m), 1468 (m), 1330 (m), 1170 (m) cm<sup>-1</sup>.

MS (EI) m/e (relative intensity): 303 (M<sup>+</sup>, 23), 274 (36), 168 (63), 214 (51), 159 (100), 130 (51).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 4.95 (d, J=5.6 Hz, 2H, -CH<sub>2</sub>-), 5.11 (t, J=5.6 Hz, 1H, -OH), 7.3-7.8 (m, 3H, ArH).

Analysis Calculated (C<sub>11</sub>H<sub>7</sub>Cl<sub>2</sub>NO<sub>3</sub>S): C, 43.44; H, 2.32; N, 4.60. Found: C, 43.27; H, 2.58; N, 4.49.



## EXAMPLE 6

## 5-[2-Oxo-1-(3,4-dichlorophenyl)ethylidene]-2,4-thiazolidinedione

(E)-5-[2-Hydroxy-1-(3,4-dichlorophenyl)ethylidene]-2,4-thiazolidinedione was converted to (E)-5-[2-oxo-1-(3,4-dichlorophenyl)ethylidene]-2,4-thiazolidinedione by the procedure of Example 3.

m.p. 186°–187° C.

IR (KBr): 3307 (bd), 1751 (m), 1671 (s), 1560 (m), 1241 (m), 791 (m)  $\text{cm}^{-1}$ .

MS (EI) m/e (relative intensity): 301 ( $\text{M}^+$ , 6), 204 (22), 202 (32).

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  7.30 (dd,  $J=1.9$ , 8.3 Hz, 1H, ArH), 7.58 (d,  $J=1.9$  Hz, 1H, ArH), 7.76 (d,  $J=8.3$  Hz, 1H, ArH), 10.68 (s, 1H, —CHO).

Analysis Calculated ( $\text{C}_{11}\text{H}_5\text{Cl}_2\text{NO}_3\text{S}$ ): C, 43.74; H, 1.67; N, 4.64. Found: C, 43.44; H, 2.00; N, 4.57.

## EXAMPLE 7

## 5-[2-Hydroxy-1-phenylpropylidene]-2,4-thiazolidinedione

The Z-isomer of the title compound was prepared from 2,4-thiazolidinedione and 2-bromopropiophenone according to the procedure of Example 1.

m.p. 199°–200° C.

IR (KBr): 3465 (bd), 1719 (s), 1675 (s), 1610 (m), 1310 (s), 1168 (m), 750 (m)  $\text{cm}^{-1}$ .

MS (CI) m/e (relative intensity): 250 ( $\text{M}+\text{H}$ , 100), 232 (74), 161 (72).

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  1.08 (d,  $J=6.67$  Hz, 3H, — $\text{CH}_3$ ), 4.4–4.5 (m, 1H, —CH—), 6.0 (d,  $J=3.5$  Hz, 1H, —OH), 7.1–7.4 (m, 5H, ArH).

Analysis Calculated ( $\text{C}_{12}\text{H}_{10}\text{NO}_3\text{S}$ ): C, 58.07; H, 4.06; N, 5.64. Found: C, 57.91; H, 4.05; N, 5.69.

## EXAMPLE 8

## 5-[2-Hydroxy-1-(naphthalenyl)ethylidene]-3-methyl-2,4-thiazolidinedione

(E)-5-[2-Hydroxy-1-(1-naphthalenyl)ethylidene]-2,4-thiazolidinedione (1.49 g, 5.22 mmol) was added to suspension of potassium carbonate (7.22 g, 52.2 mmol) in acetone. After 30 minutes iodomethane (0.65 mL, 10.4 mmol) was added. After 30 min the mixture was filtered, and concentrated to give a brown oil which was dissolved in chloroform. The resulting solution was washed with water then dried over magnesium sulfate and concentrated in vacuo to give an oil which was chromatographed on silica gel (chloroform/acetone/nitrile) to give a glass (1.17 g). Recrystallization from carbon tetrachloride/hexane/ether gave analytically pure E isomer of the title compound as yellow needles (0.90 g).

m.p. 112°–113° C.

IR (KBr): 3520 (bd), 1735 (s), 1668 (s), 1592 (m), 1367 (s), 1140 (m), 777 (s)  $\text{cm}^{-1}$ .

MS (EI) m/e (relative intensity): 299 ( $\text{M}^+$ , 100), 270 (44), 213 (15), 196 (19), 185 (31), 153 (39), 152 (66), 141 (44), 128 (40).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  3.26 (s, 3H, — $\text{NCH}_3$ ), 4.47 (dd,  $J=8.9$ , 6.7 Hz, 1H, —OH), 4.74 (dd,  $J=14.6$ , 8.9 Hz, 1H, —CHH—), 4.87 (dd,  $J=14.6$ , 6.7 Hz, 1H, —CHH—), 7.34–7.94 (m, 7H, ArH).

Analysis Calculated ( $\text{C}_{16}\text{H}_{13}\text{NO}_3\text{S}$ ): C, 64.17; H, 4.34; N, 4.68. Found: C, 64.08; H, 4.51; N, 4.61.

## EXAMPLE 9

## 5-[2-Methoxy-1-(naphthalenyl)ethylidene]-2,4-thiazolidinedione

(E)-5-[2-Hydroxy-1-(1-naphthalenyl)ethylidene]-2,4-thiazolidinedione (1.50 g) was dissolved in tetrahydrofuran (25 mL) and treated with Hunig's base (1.41 mL). After 10 min 2-(trimethylsilyl)ethoxymethyl chloride (1.0 mL) was added. After 1 h aqueous hydrochloric acid (1.0N) was added and the tetrahydrofuran removed in vacuo. The aqueous phase was washed with ether and the ether phase washed with aqueous hydrochloric acid (1.0N) (2 $\times$ ) and 5% aqueous sodium bicarbonate (3 $\times$ ). The ether phase was dried over magnesium sulfate and concentrated in vacuo to give (E)-5-[2-hydroxy-1-(naphthalen-1-yl)ethylidene]-3-[2-(trimethylsilyl)ethoxymethyl]-2,4-thiazolidinedione as an orange oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  —0.03 (s, 9H, — $\text{Si}(\text{CH}_3)_3$ ), 0.97 (t,  $J=8$  Hz, 2H, — $\text{OCH}_2\text{CH}_2$ —), 3.68 (t,  $J=8$  Hz, 2H, — $\text{OCH}_2\text{CH}_2$ —), 4.28 (t,  $J=7$  Hz, 1H, —OH), 4.64–4.96 (m, 2H, — $\text{CH}_2\text{OH}$ ), 5.11 (s, 2H,  $\text{NCH}_2\text{O}$ ), 7.3–8.0 (m, 7H, ArH).

The above material was dissolved in dichloromethane (25 mL) and treated with triethylamine (1.1 mL). The mixture was cooled to —78° C. and treated with methanesulfonyl chloride (0.57 mL). After 1 h the reaction mixture was allowed to warm to 25° C. and washed with 1N aqueous hydrochloric acid (3 $\times$ ) and 5% aqueous sodium bicarbonate (3 $\times$ ). The organic layer was dried over magnesium sulfate and concentrated in vacuo to give methanesulfonic acid 2-{2,4-dioxo-3-[2-(trimethylsilyl)ethoxymethyl]-thiazolidin-5-ylidene}-2-naphthalen-1-yl-ethyl ester E-isomer as a yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  0.0 (s, 9H, — $\text{Si}(\text{CH}_3)_3$ ), 0.98 (t,  $J=8$  Hz, 2H, — $\text{OCH}_2\text{CH}_2$ —), 2.67 (s, 3H, — $\text{SO}_2\text{CH}_3$ ), 3.68 (t,  $J=8$  Hz, 2H, — $\text{OCH}_2\text{CH}_2$ —), 5.12 (s, 2H,  $\text{NCH}_2\text{O}$ ), 5.70 (d,  $J=13$  Hz, 1H, — $\text{CHHOSO}_2\text{Me}$ ), 5.96 (d,  $J=13$  Hz, 1H, — $\text{CHHOSO}_2\text{Me}$ ), 7.3–8.0 (m, 7H, ArH).

The above material was dissolved in methanol (50 mL) and heated at reflux for 1 h. Methanesulfonic acid (5 mL) was added and the resulting solution was heated at reflux for 6 h then cooled to 25° C. Aqueous potassium hydroxide (1.0N) was added until the mixture was basic. Methanol was removed in vacuo and the resulting mixture acidified with aqueous hydrochloric acid (2.0N). Extraction with ether (3 $\times$ ), drying of the combined ether layers with magnesium sulfate and concentration gave a yellow foam (1.29 g). Chromatography and recrystallization (hexane/ethyl acetate/ether) gave analytically pure (E)-5-[2-methoxy-1-(1-naphthalenyl)ethylidene]-2,4-thiazolidinedione as yellow crystals (0.38 g).

m.p. 133°–134° C.

IR (KBr): 3430 (bd), 3155 (m), 3019 (m), 1733 (s), 1683 (s), 1610 (m), 1323 (s), 1070 (m), 769 (s)  $\text{cm}^{-1}$ .

MS (EI) m/e (relative intensity): 299 ( $\text{M}^+$ , 62), 222 (14), 213 (22), 196 (72), 195 (67), 183 (39), 165 (31), 152 (100), 139 (64).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  3.29 (s, 3H, — $\text{OCH}_3$ ), 4.94 (d,  $J=14.0$  Hz, 1H, —CHH—), 5.14 (d,  $J=14.0$  Hz, 1H, —CHH—), 7.3–8.0 (m, 7H, ArH), 8.42 (bd s, 1H, —NH).

Analysis Calculated ( $\text{C}_{16}\text{H}_{13}\text{NO}_3\text{S}$ ): C, 64.17; H, 4.34; N, 4.68. Found: C, 64.22; H, 4.43; N, 4.65.



## Pharmacology

On the morning of Day 1, 12-15 mice [male db/db (C57BL/KsJ), Jackson Laboratories, 2 to 7 months of age and body weight 35 to 60 g] were fasted for 4 hours, weighed and a baseline blood sample was collected from the tail-tip of each mouse without anesthesia, placed directly into a fluoride-containing tube, mixed and maintained on ice. Food was then returned to the mice. The plasma was separated and levels of glucose in plasma determined by the Abbott VP Analyzer. Because of the variable plasma glucose levels of the db/db mice, the mice were randomly assigned into 3-5 groups (4-5 mice per group) of equivalent mean plasma glucose levels:

- Group A: Vehicle control
- Group B: Positive control (ciglitazone)
- Group C: 1st Test drug
- Group D: 2nd Test drug
- Group E: 3rd Test drug

On the afternoon of Days 1, 2 and 3 the vehicle, control or test drugs were administered (p.o.) to the ad libitum fed mice. The positive control, ciglitazone {(±)-5-[4-[(1-methylcyclohexyl)benzyl]thiazolidine-2,4-dione, Fujita et al., Diabetes 1983, 30, 804}, was given by gavage at a dose of 100 mg/kg/day. The test compounds were given by gavage at a dose of 100 mg/kg/day. The fourth and final dose was administered on the morning of day 4, after the mice had been fasted for 18 h. A blood sample was collected immediately preceding the last dose, followed by samples collected at 90 and 120 min after drug administration. Insulin is immediately administered to each mouse after the 120 min sample. Serial blood samples were collected at 45 and 120 min after insulin administration. The plasma was separated and the levels of glucose in plasma determined by the Abbott VP analyzer.

Analysis of variance followed by Dunnett's multiple comparison (one-sided) was used to estimate the degree of statistical significance of the difference between the vehicle control group and the individual drug-treated groups. A drug was considered active, at the specific dose administered, if the difference of the plasma glucose level has a  $p < 0.10$ .

The actual difference between the mean percent change of blood glucose levels of the vehicle and the drug-treated group is reported in Table 1. Examination of the results tabulated in Table 1 shows that the compounds of this invention are well suited as antidiabetic agents for they lower blood glucose levels in diabetic (db/db) mice. For example, (E)-5-[2-oxo-1-(3,4-dichlorophenyl)ethylidene]-2,4-thiazolidinedione, the E-isomer of the compound of Example 6, effects a lowering of blood glucose levels comparable to that of ciglitazone at an identical dose of 100 mg/kg.

TABLE 1

Compound of	Isomer	Blood Glucose Levels % Change From Vehicle (100 mg/kg)
Example 1	E	-28
Example 2	E	-19
Example 3	E	-21
Example 4	E	-25
Example 5	E	-31
Example 6	E	-47
Example 7	Z	-23
Example 8	E	-27
Example 9	E	-24
Ciglitazone		-24 to -50

TABLE 1-continued

Compound of	Isomer	Blood Glucose Levels % Change From Vehicle (100 mg/kg)
(Positive Control)		

## Pharmaceutical Composition

Based on the results of the pharmacological assay, the compounds of this invention are useful in the treatment of hyperglycemia in diabetes mellitus.

The compounds may be administered neat or with a pharmaceutical carrier to a mammal in need thereof.

The pharmaceutical carrier may be solid or liquid and the active compound shall be a therapeutically effective amount.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compound can also be administered orally either in liquid or solid composition form.

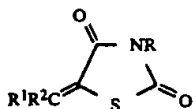
Preferable, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for exam-



ple, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. The dosage to be used in the treatment must be subjectively determined by the attending physician.

What is claimed is:

1. A compound according to the formula:



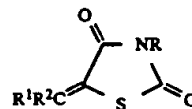
wherein:

- R is H or lower alkyl,  
 R¹ is phenyl, 2,3-dichlorophenyl, naphthalenyl or 5-methyl-1-naphthalenyl;  
 R² is R³—X— where X is —CO— or —CHOR⁴— when X is CHOR⁴, R³ is H, lower alkyl, or aryl where aryl is phenyl or naphthalenyl; optionally substituted by halogen, lower alkyl or lower alkoxy and when X is —CO—, R³ is H;  
 R⁴ is H or methyl;  
 or a solvate or a pharmaceutically acceptable cationic salt thereof;  
 and R¹ and R² may be in the E or Z configuration with respect to the 2,4-thiazolidinedione ring.  
 2. A compound according to claim 1 wherein R is H or methyl,  
 R¹ is phenyl, 2,3-dichlorophenyl, naphthalenyl, or 5-methyl-1-naphthalenyl  
 R³ is H, methyl or phenyl optionally substituted by halogen, lower alkyl or lower alkoxy; and  
 R⁴ is H or methyl.  
 3. A compound according to claim 1 which is 5-[2-hydroxy-1-(1-naphthalenyl)ethylidene]-2,4-thiazolidinedione or a pharmaceutically acceptable salt thereof.  
 4. A compound according to claim 1 which is 5-[2-hydroxy-1-(5-methylnaphthalen-1-yl)ethylidene]-2,4-thiazolidinedione or a pharmaceutically acceptable salt thereof.  
 5. A compound according to claim 1 which is 5-[2-oxo-1-(1-naphthalenyl)ethylidene]-2,4-thiazolidinedione or a pharmaceutically acceptable salt thereof.  
 6. A compound according to claim 1 which is 5-[2-hydroxy-1,2-diphenylethylidene]-2,4-thiazolidinedione or a pharmaceutically acceptable salt thereof.  
 7. A compound according to claim 1 which is 5-[2-hydroxy-1-(3,4-dichlorophenyl)ethylidene]-2,4-thiazolidinedione or a pharmaceutically acceptable salt thereof.  
 8. A compound according to claim 1 which is 5-[2-oxo-1-(3,4-dichlorophenyl)ethylidene]-2,4-thiazolidinedione or a pharmaceutically acceptable salt thereof.  
 9. A compound according to claim 1 which is 5-[2-hydroxy-1-phenylpropylidene]-2,4-thiazolidinedione or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 which is 5-[2-hydroxy-1-(1-naphthalenyl)ethylidene]-3-methyl-2,4-thiazolidinedione.

11. A compound according to claim 1 which is 5-[2-methoxy-1-(1-naphthalenyl)ethylidene]-2,4-thiazolidinedione.

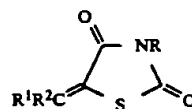
12. A method of treating hyperglycemia in diabetes mellitus which comprises administration to a mammal in need thereof a therapeutically effective amount of a compound according to the formula:



wherein:

- R is H or lower alkyl,  
 R¹ is phenyl, 2,3-dichlorophenyl, naphthalenyl or 5-methyl-1-naphthalenyl;  
 R² is R³—X— where X is —CO— or —CHOR⁴— and when X is CHOR⁴, R³ is H, lower alkyl, or aryl where aryl is phenyl or naphthalenyl, optionally substituted by halogen, lower alkyl or lower alkoxy and when X is —CO—, R³ is H;  
 R⁴ is H or methyl;  
 or a solvate or a pharmaceutically acceptable cationic salt thereof;  
 and R¹ and R² may be in the E or Z configuration with respect to the 2,4-thiazolidinedione ring.  
 13. A method according to claim 12 where, in the compound used, R is H or methyl, R¹ is phenyl, 2,3-dichlorophenyl, naphthalenyl, or 5-methyl-1-naphthalenyl, R³ is H, methyl or phenyl optionally substituted by halogen, lower alkyl or lower alkoxy; and R⁴ is H or methyl.

14. A pharmaceutical composition for the treatment of hyperglycemia in diabetes mellitus which comprises a pharmaceutical carrier and a therapeutically effective amount of a compound having the formula:



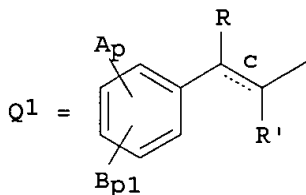
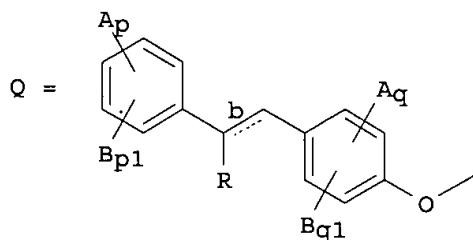
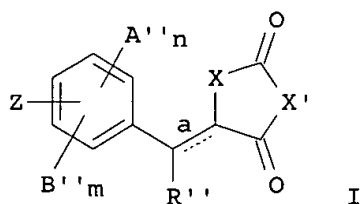
wherein:

- R is H or lower alkyl,  
 R¹ is phenyl, 2,3-dichlorophenyl, naphthalenyl or 5-methyl-1-naphthalenyl;  
 R² is R³—X— where X is —CO— or —CHOR⁴— and when X is CHOR⁴, R³ is H, lower alkyl, or aryl where aryl is phenyl or naphthalenyl, optionally substituted by halogen, lower alkyl or lower alkoxy and when X is —CO—, R³ is H;  
 R⁴ is H or methyl;  
 or a solvate or a pharmaceutically acceptable cationic salt thereof;  
 and R¹ and R² may be in the E or Z configuration with respect to the 2,4-thiazolidinedione ring.



BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2001066670	A5	20011224	AU 2001-66670	20010605
PRAI US 1998-74925	A2	19980508		
US 1999-287237	A2	19990406		
US 2000-591105	A2	20000609		
US 2001-785554	A2	20010220		
US 2001-843167	A2	20010427		
WO 2001-US17950	W	20010605		
OS MARPAT 136:247571				
GI				

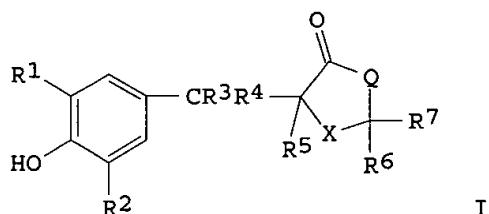


AB Novel diphenylethylene compds. and derivs. thereof contg. thiazolidinedione or oxazolidinedione moieties are provided which are effective in lowering blood glucose level, serum insulin, triglyceride and free fatty acid levels in animal models of Type II **diabetes**. The above compds. and their derivs. are resented by formula [I; Z = Q, Q1, H, A'', B''; wherein n, m, q, q1 = integers from zero to 4 provided that  $n+m \leq 4$  and  $q+q1 \leq 4$ ; p, p1 = integers from zero to 5 provided that  $p+p1 \leq 5$ ; a, b and c are double bonds which may be present or absent; when present; the double bonds may be in the E or Z configuration and, when absent, the resulting stereocenters may have the R- or S-configuration; R, R', R'' = H, C1-20 linear or branched alkyl, C2-20 linear or branched alkenyl, CO2Z' (wherein Z' = H, Na, K, or other pharmaceutically acceptable counterion such as Ca, Mg, ammonium, tromethamine, and the like), CO2R''', NH2, NHR''', N(R''')2, OH, OR''', halo, substituted C1-20 linear or branched alkyl or substituted C2-20 linear or branched alkenyl (wherein R''' is C1-20 linear or branched alkyl or linear or branched alkenyl); A, A', A'' = H, C1-20 acylamino, C1-20 acyloxy, C1-20 alkanoyl, C1-20 alkoxycarbonyl, C1-20 alkoxy, C1-20 alkylamino, C1-20 alkylcarboxylamino, CO2H, cyano, halo, HO; B, B', B'' = H, C1-20 acylamino, C1-20 acyloxy, C1-20 alkanoyl, C1-20 alkenoyl, C1-20 alkoxycarbonyl, C1-20 alkoxy, C1-20 alkylamino, C1-20 alkylcarboxylamino, aroyl, aralkanoyl, CO2H, cyano, halo, HO; or A and B together, or A' and B' together, or A'' and B'' together, may be joined to form a methylenedioxy or ethylenedioxy group; and X, X' are independently -NH, -NR''', O or S]. In contrast to previously reported thiazolidinedione compds., known to lower leptin levels, the present compds. increase leptin levels and have no known liver toxicity. They inhibit the activity of TNF-alpha, interleukin IL-1 or IL-6 or cyclooxygenase-2 (COX-2). The



AN 1993:6969 CAPLUS  
 DN 118:6969  
 TI Preparation of aryl-substituted rhodanine derivatives for the treatment of type I **diabetes**  
 IN Lafferty, Kevin John; Panetta, Jill Ann  
 PA University of Colorado Foundation, Inc., USA  
 SO Eur. Pat. Appl., 45 pp.  
 CODEN: EPXXDW  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 500337	A1	19920826	EP 1992-301351	19920219
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE				
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	ZA 9201108	A	19930814	ZA 1992-1108	19920214
	CA 2061363	AA	19920823	CA 1992-2061363	19920217
	AU 9211114	A1	19920827	AU 1992-11114	19920220
	AU 651865	B2	19940804		
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OS	MARPAT 118:6969				
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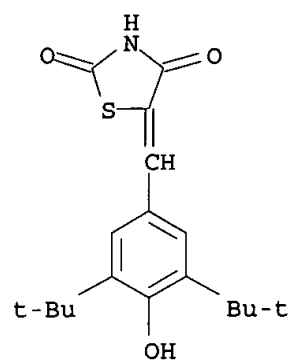


AB Title compds. I (R1, R2 = H, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C1-4-alkyl-O2C-C14-alkyl, PhS(CH2)n; n = 0-3; R3 = H, C1-6 alkyl; R4, R5 = H, R4R5 = bond; R6, R7 = H, or when one of R6, R7 = H the other is HO, MeS; R6R7 = S, O; X = S(O)m wherein m = 0-2; Q = CH2, O, R8N wherein R8 = H, C1-6 alkyl, C2-6 alkenyl, etc.) are prepd.  
 3,5,4-(Me3C)2(HO)C6H2CHO, rhodamine, and fused NaOAc were refluxed to give I (R1 = R2 = Me3C, R3 = R4 = R5 = H, R6R7 = X = S) (II). II in EtOH was hydrogenated in presence of Pd/C to give I (R1 = R2 = Me3C, R3-R7 = H, Q = HN, X = S) (III). Mice given 250 mg/kg cyclophosphamide (IV) and fed a diet contg. 0.1 wt.% III one day prior to IV and continued for 21 days, resulted in 5/17 animals developing **diabetes**. Pharmaceutical formulations comprising I are given.

IT 127378-46-5P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of, as antidiabetic)

RN 127378-46-5 CAPLUS  
 CN 2,4-Thiazolidinedione, 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]- (9CI) (CA INDEX NAME)







09-11-11

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(FILE 'HOME' ENTERED AT 08:19:42 ON 02 APR 2003)

FILE 'REGISTRY' ENTERED AT 08:19:51 ON 02 APR 2003

L1 STRUCTURE UPLOADED

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L3 17 S L1 FUL

FILE 'CAPLUS' ENTERED AT 08:20:42 ON 02 APR 2003

L4 6 S L3

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L1 HAS NO ANSWERS

L1 STR

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

Structure attributes must be viewed using STN Express query preparation.

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L4 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS

AN 2002:185699 CAPLUS

DN 136:247571

TI Preparation of novel heterocyclic analogs of diphenylethylene compounds as inhibitors of cytokines or cyclooxygenase

IN Nag, Bishwajit; Dey, Debendranath; Medicherla, Satyanarayana; Neogi, Partha

PA USA

SO U.S. Pat. Appl. Publ., 34 pp., Cont.-in-part of U.S. Ser. No. 785,554.

CODEN: USXXCO

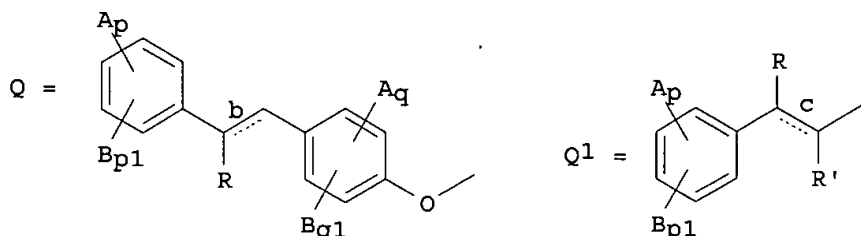
DT Patent

LA English

FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002032225	A1	20020314	US 2001-843167	20010427
	US 6245814	B1	20010612	US 1998-74925	19980508
	US 2002025975	A1	20020228	US 2001-785554	20010220
	WO 2001095859	A2	20011220	WO 2001-US17950	20010605
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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PRAI	US 1998-74925	A2	19980508		
	US 1999-287237	A2	19990406		
	US 2000-591105	A2	20000609		
	US 2001-785554	A2	20010220		
	US 2001-843167	A2	20010427		
	WO 2001-US17950	W	20010605		
OS	MARPAT 136:247571				
GI					





Novel diphenylthylene compounds. and derivs. thereof contg. thiazolidinedione or oxazolidinedione moieties are provided which are effective in lowering blood glucose level, serum insulin, triglyceride and free fatty acid levels in animal models of Type II diabetes. The above compds. and their derivs. are resented by formula [I; Z = Q, Q1, H, A", B"; wherein n, m, q, q1 = integers from zero to 4 provided that n+m.ltoreq.4 and q+q1.ltoreq.4; p, p1 = integers from zero to 5 provided that p+p1.ltoreq.5; a, b and c are double bonds which may be present or absent; when present, the double bonds may be in the E or Z configuration and, when absent, the resulting stereocenters may have the R- or S-configuration; R, R', R" = H, C1-20 linear or branched alkyl, C2-20 linear or branched alkenyl, CO2Z' (wherein Z' = H, Na, K, or other pharmaceutically acceptable counterion such as Ca, Mg, ammonium, tromethamine, and the like), CO2R''', NH2, NHR''', N(R''')2, OH, OR''', halo, substituted C1-20 linear or branched alkyl or substituted C2-20 linear or branched alkenyl (wherein R''' is C1-20 linear or branched alkyl or linear or branched alkenyl); A, A', A'' = H, C1-20 acylamino, C1-20 acyloxy, C1-20 alkanoyl, C1-20 alkoxycarbonyl, C1-20 alkoxy, C1-20 alkylamino, C1-20 alkylcarboxylamino, CO2H, cyano, halo, HO; B, B', B'' = H, C1-20 acylamino, C1-20 acyloxy, C1-20 alkanoyl, C1-20 alkenoyl, C1-20 alkoxycarbonyl, C1-20 alkoxy, C1-20 alkylamino, C1-20 alkylcarboxylamino, aroyl, aralkanoyl, CO2H, cyano, halo, HO; or A and B together, or A' and B' together, or A'' and B'' together, may be joined to form a methylenedioxy or ethylenedioxy group; and X, X' are independently -NH, -NR''', O or S]. In contrast to previously reported thiazolidinedione compds., known to lower leptin levels, the present compds. increase leptin levels and have no known liver toxicity. They inhibit the activity of TNF-alpha, interleukin IL-1 or IL-6 or cyclooxygenase-2 (COX-2). The compds. are disclosed as useful for a variety of treatments including the treatment of inflammation, inflammatory and immunol. diseases, insulin resistance, hyperlipidemia, coronary artery disease, cancer and multiple sclerosis. Thus, To a mixt. of 3,5-dimethoxybenzaldehyde (500 g) and p-hydroxyphenylacetic acid (457 g) was added acetic anhydride (1 L) and triethylamine (420 mL) and the nonhomogeneous mixt. on heating became homogeneous at 70.degree. and stirred at 130-140.degree. for 6 h to give 47% 3-(3,5-dimethoxyphenyl)-2-(4-hydroxyphenyl)acrylic acid (II) (428 g). II (427.5 g) was suspended in 3 L methanol, treated with 100 mL concd. H2SO4, and heated at reflux for 20 h under Ar to give 97% 3-(3,5-dimethoxyphenyl)-2-(4-hydroxyphenyl)acrylic acid Me ester (III). III (433 g) was dissolved in 1.6 L DMF, treated with 60.4 g NaH (50% in



oil) and the with 185 mL p-fluorobenzaldehyde, and heated at 180.degree. for 18 h to give 77% 3-(3,5-dimethoxyphenyl)-2-[4-(4-formylphenoxy)phenyl]acrylic acid Me ester which (352 g), 2,4-thiazolidinedione 98.6, benzoic acid 134, and piperidine 107.4 g were heated in 2.5 L toluene at reflux with continuous removal of H<sub>2</sub>O through Dean-Stark app. to give 86% 3-(3,5-dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]phenyl]acrylic acid Me ester (IV). IV (30 g) was hydrogenated over 15 g 10% Pd-C in 900 mL dioxane in a Parr app. at 60 Psi for 24 h, followed by adding 15 g 10% Pd-C and continuing the hydrogenation for another 24 h to give 86% 3-(3,5-dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]phenyl]acrylic acid Me ester (V). When V was orally administered to ob/ob mice with a single oral dose (50 mg/kg body wt.), there was a 62 % drop in blood glucose level and, similar to db/db mice, there was no significant increase in body wt. between the control and the treatment groups. This was in contrast to treatment of diabetic animals by thiazolidinedione type compds. which are known to be assocd. with increase in body wt.

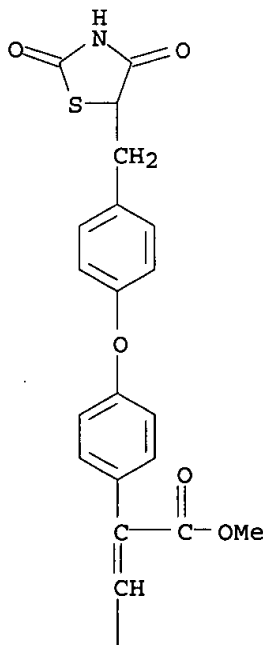
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 380881-31-2P, 3-(3,5-Dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]phenyl]acrylic acid methyl ester  
 RL: IMF (Industrial manufacture); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of novel heterocyclic analogs of phenylethylene compds. as inhibitors of cytokines or cyclooxygenase for therapeutic agents)

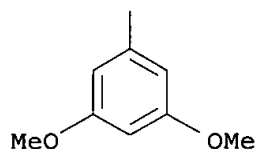
RN 249886-47-3 CAPLUS

CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]-, methyl ester (9CI) (CA INDEX NAME)

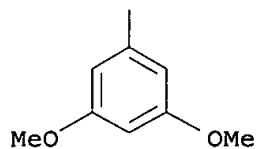
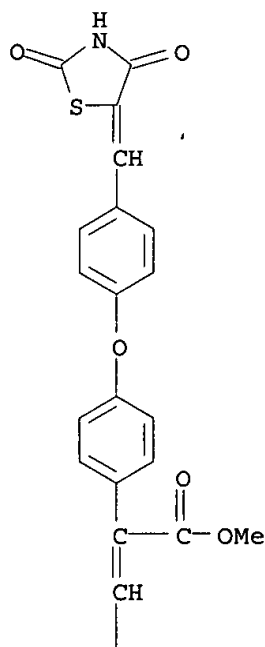
PAGE 1-A







RN 380881-31-2 CAPLUS  
 CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenoxy]-, methyl ester (9CI) (CA INDEX NAME)

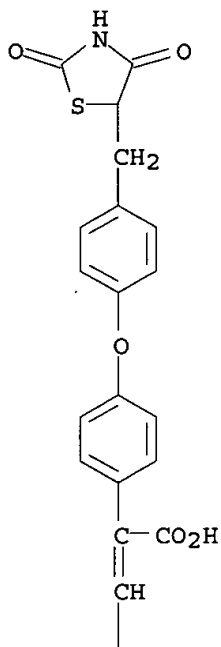


IT 380881-35-6P, 3-(3,5-Dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]phenyl]acrylic acid  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (prepn. of novel heterocyclic analogs of phenylethylene compds. as inhibitors of cytokines or cyclooxygenase for therapeutic agents)  
 RN 380881-35-6 CAPLUS

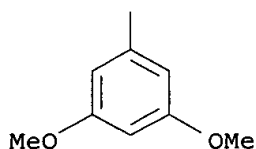


CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



IT **380881-37-8P**, 3-(3,5-Dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]phenyl]acrylamide **380881-39-0P**, 3-(3,5-Dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]phenyl]-N,N-dimethylacrylamide **380881-41-4P**, 3-(3,5-Dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]phenyl]-N-methoxy-N-methylacrylamide **380881-47-0P**, 3-(3,5-Dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]phenyl]propionic acid methyl ester **380881-49-2P**, 3-(3,5-Dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]phenyl]propionic acid **380881-51-6P**, 3-(3,5-Dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]phenyl]propionic acid methyl ester **380881-53-8P**, 3-(3,5-Dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]phenyl]propionic acid **380881-55-0P**, 3-(3,5-Dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]phenyl]acrylic acid  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of novel heterocyclic analogs of phenylethylene compds. as



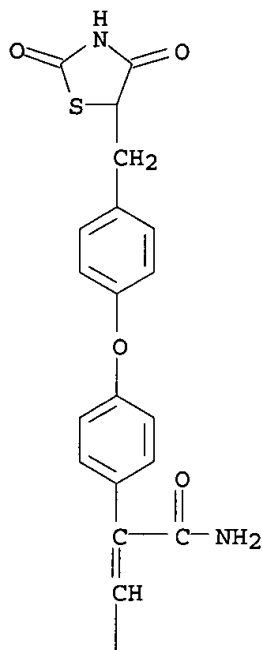
09/584,952

inhibitors of cytokines or cyclooxygenase for therapeutic agents)

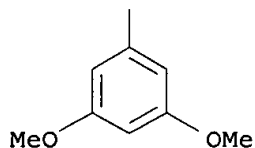
RN 380881-37-8 CAPLUS

CN Benzeneacetamide, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]- (9CI) (CA INDEX NAME)

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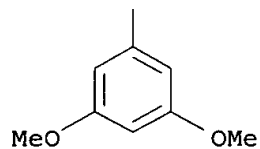
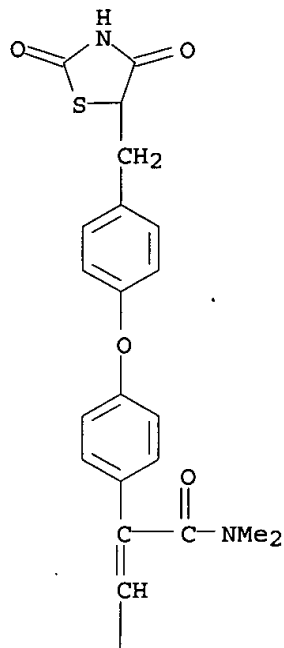
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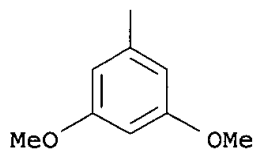
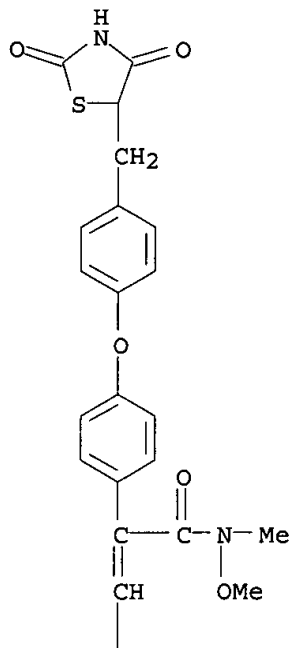
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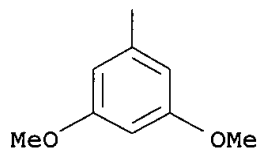
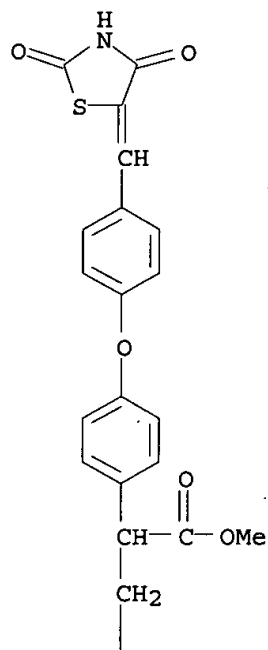
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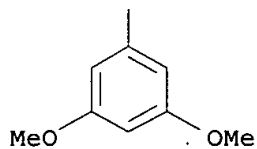
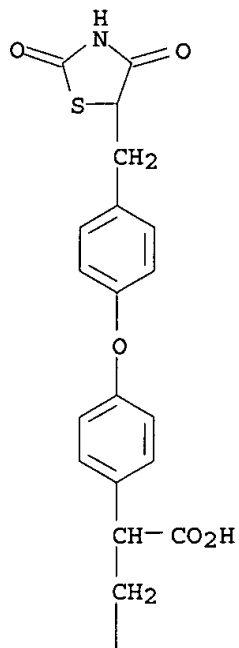
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 CN Benzenepropanoic acid, .alpha.-[4-[4-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenoxy]phenyl]-3,5-dimethoxy-, methyl ester  
 (9CI) (CA INDEX NAME)





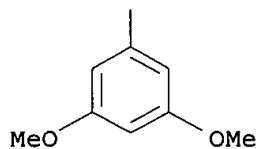
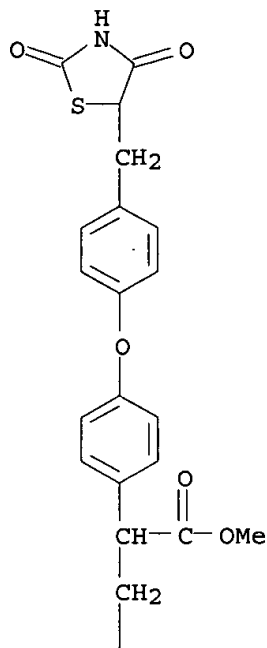
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CN Benzenepropanoic acid, .alpha.-[4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]phenyl]-3,5-dimethoxy- (9CI) (CA INDEX NAME)





RN 380881-51-6 CAPLUS  
CN Benzenepropanoic acid, .alpha.-[4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]phenyl]-3,5-dimethoxy-, methyl ester (9CI)  
(CA INDEX NAME)



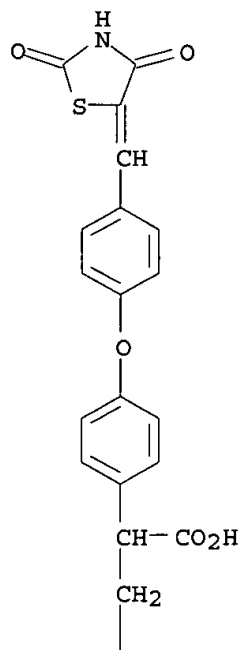


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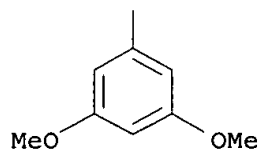


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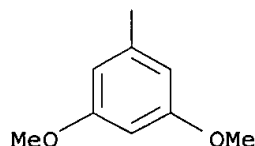
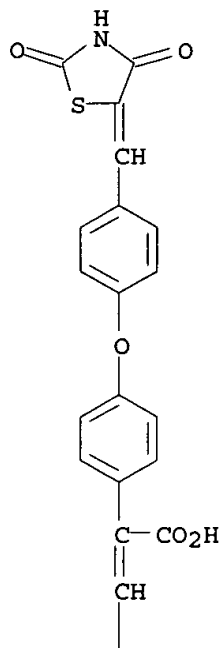


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RN 380881-55-0 CAPLUS  
CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenoxy]- (9CI) (CA INDEX NAME)





L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS  
 AN 2002:158391 CAPLUS  
 DN 136:216745  
 TI Preparation and activity of diphenylethylene thiazolidinediones and  
 analogs as antidiabetics, antiinflammatories, or immunomodulators  
 IN Nag, Bishwajit; Dey, Debendranath; Medicherla, Satyanarayana; Neogi,  
 Partha  
 PA USA  
 SO U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of U.S. Ser. No. 591,105.  
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 DT Patent  
 LA English  
 FAN.CNT 5

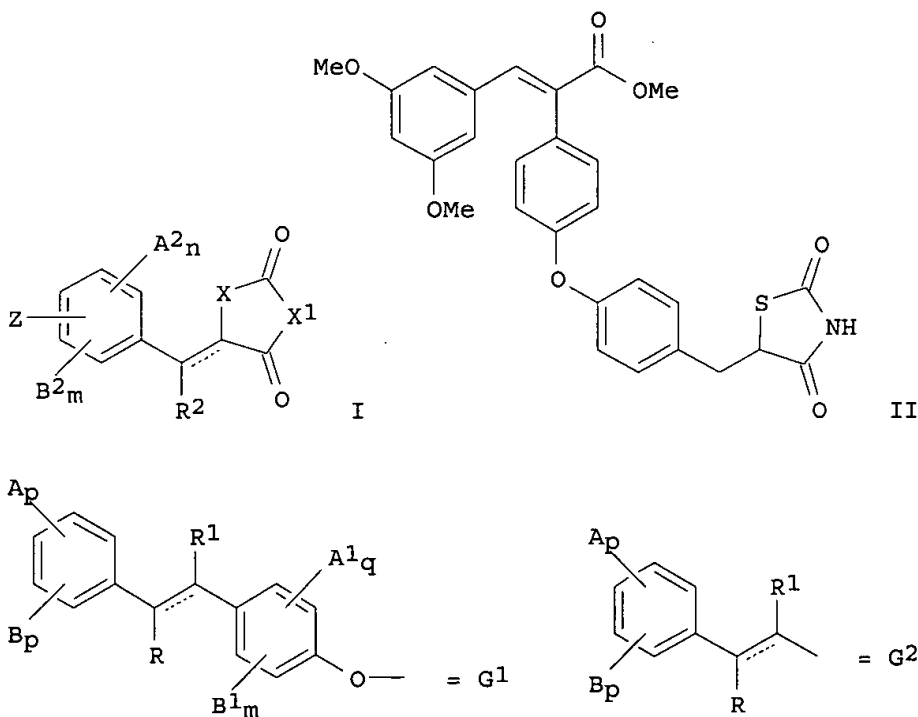
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	US 2002032225	A1	20020314	US 2001-843167	20010427
	WO 2001095859	A2	20011220	WO 2001-US17950	20010605

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 OS MARPAT 136:216745  
 GI



AB Title compds. I [wherein Z = G1, H, A2, B2, or G2; n, m, and q = independently 0-4; p = independently 0-5; R, R1, and R2 = independently H, (un)substituted alkyl or alkenyl, CO<sub>2</sub>Z1, CO<sub>2</sub>R3, NH<sub>2</sub>, NHR3, NR32, OH, OR3, or halo; Z1 = H, Na, K, or other pharmaceutically acceptable counterion; R3 = alkyl or alkenyl; A, A1, and A2 = independently H, acylamino, acyloxy, alkanoyl, alkoxy, alkoxy, alkylamino, alkylcarboxylamino, carboxyl, CN, H, or OH; B, B1, and B2 = independently H, acylamino, acyloxy, alkanoyl, alkenoyl, alkoxy, alkylamino, alkylcarboxylamino, aroyl, aralkanoyl, carboxyl, CN, halo, or OH; or A and B or A1 and B1 or A2 and B2 together form a methylenedioxy or ethylenedioxy group; X and X1 = independently NH, NR3, O, or S] are provided which are effective in lowering blood glucose level, serum insulin, triglyceride, and free fatty acid levels in animal models of Type II diabetes. In contrast to previously reported thiazolidinedione compds., known to lower leptin levels, the present compds. increase leptin



levels and have no known liver toxicity. Thus, II was prepd. in five steps by condensation of 3,5-dimethoxybenzaldehyde with 4-hydroxyphenylacetic acid (47%), followed by esterification (97%), etherification with 4-fluorobenzaldehyde (77%), condensation with 2,4-thiazolidinedione (86%), and hydrogenation of the ylidene double bond (40%). Oral administration of II to obese mice caused a 62% drop in blood glucose level. I are useful for the treatment of inflammation, inflammatory and immunol. diseases, insulin resistance, hyperlipidemia, coronary artery disease, cancer, and multiple sclerosis.

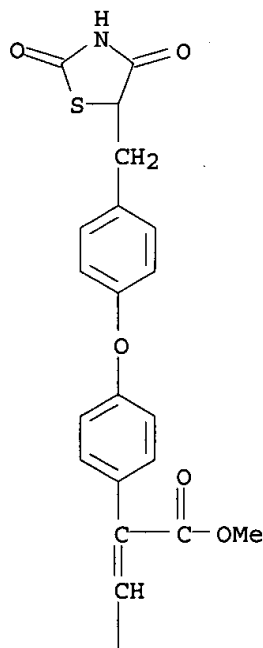
IT 249886-47-3P

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(prepn. and activity of diphenylethylene thiazolidinediones and analogs as antidiabetics, antiinflammatories, or immunomodulators)

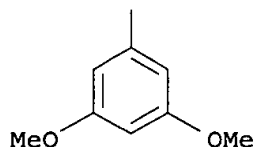
RN 249886-47-3 CAPLUS

CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]-, methyl ester (9CI) (CA INDEX NAME)

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IT 380881-31-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)



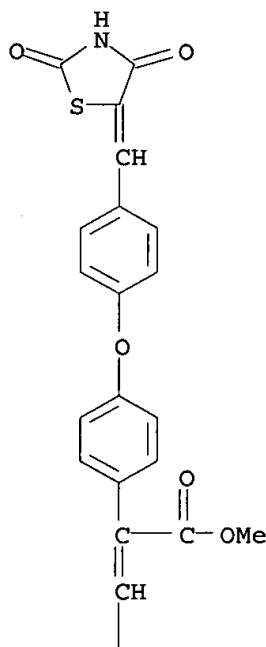
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(prepn. and activity of diphenylethylene thiazolidinediones and analogs  
as antidiabetics, antiinflammatories, or immunomodulators)

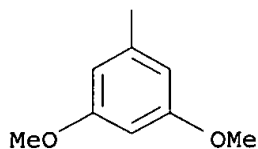
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CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-  
dioxo-5-thiazolidinylidene)methyl]phenoxy]-, methyl ester (9CI) (CA INDEX  
NAME)

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PAGE 2-A



L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS

AN 2001:923567 CAPLUS

DN 136:37596

TI Preparation and activity of diphenylethylene thiazolidinedione or  
oxazolidinedione compounds as antidiabetics or antiinflammatories

IN Neogi, Partha; Nag, Bishwajit; Medicherla, Satyanarayana; Dey,  
Debendranath

PA Calyx Therapeutics, Inc., USA

SO PCT Int. Appl., 76 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 5

PATENT NO.

KIND

DATE

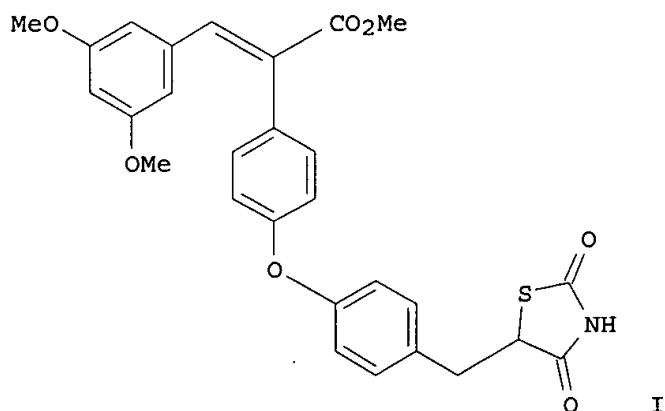
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DATE

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 OS MARPAT 136:37596  
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AB Novel diphenylethylene compds. and derivs. thereof contg.  
 thiazolidinedione or oxazolidinedione moieties are provided which are  
 effective in lowering blood glucose level, serum insulin, triglyceride and  
 free fatty acid levels in animal models of Type II diabetes. In contrast  
 to previously reported thiazolidinedione compds., known to lower leptin  
 levels, the present compds. increase leptin levels and have no known liver  
 toxicity. Thus, (I) was prepd. in five steps by condensation of  
 3,5-dimethoxybenzaldehyde with 4-hydroxyphenylacetic acid followed by  
 esterification and etherification with 4-fluorobenzaldehyde and  
 condensation with 2,4-thiazolidinedione and hydrogenation of the ylidene  
 double bond. Oral administration of I to obese mice caused a 62% drop in  
 blood glucose level. The compds. are disclosed as useful for a variety of  
 treatments including the treatment of inflammation, inflammatory and  
 immunol. diseases, insulin resistance, hyperlipidemia, coronary artery  
 disease, cancer and multiple sclerosis.

IT 249886-47-3P 380881-31-2P 380881-35-6P  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic  
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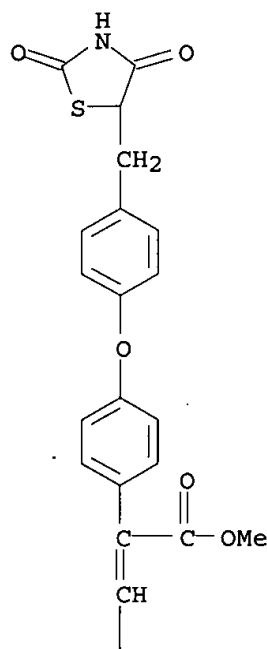
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(prepn. and activity of diphenylethylene thiazolidinedione or  
oxazolidinedione compds. as antidiabetics or antiinflammatories)

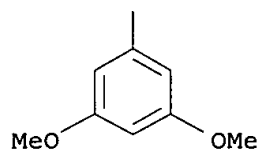
RN 249886-47-3 CAPLUS

CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-  
dioxo-5-thiazolidinyl)methyl]phenoxy]-, methyl ester (9CI) (CA INDEX  
NAME)

PAGE 1-A



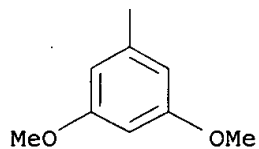
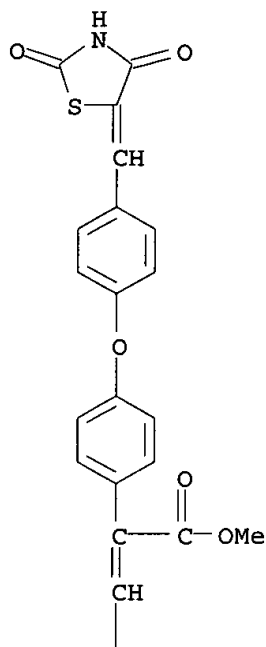
PAGE 2-A



RN 380881-31-2 CAPLUS

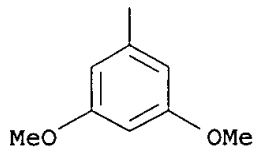
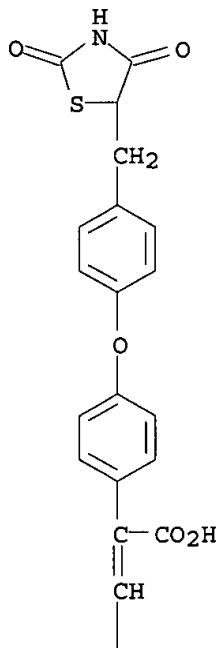
CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-  
dioxo-5-thiazolidinylidene)methyl]phenoxy]-, methyl ester (9CI) (CA INDEX  
NAME)





RN 380881-35-6 CAPLUS  
CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]- (9CI) (CA INDEX NAME)





IT 380881-37-8P 380881-39-0P 380881-41-4P  
 380881-47-0P 380881-49-2P 380881-51-6P  
 380881-53-8P 380881-55-0P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. and activity of diphenylethylene thiazolidinedione or oxazolidinedione compds. as antidiabetics or antiinflammatories)

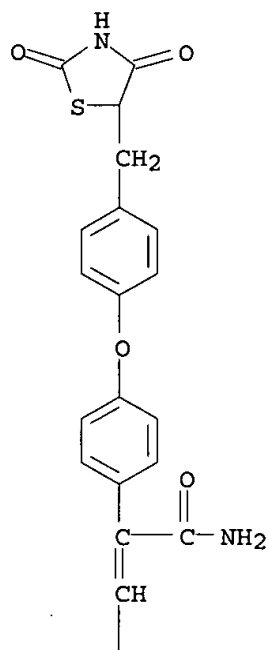
RN 380881-37-8 CAPLUS

CN Benzeneacetamide, .alpha.-[[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]- (9CI) (CA INDEX NAME)

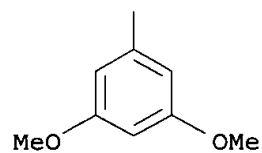


09/584,952

PAGE 1-A

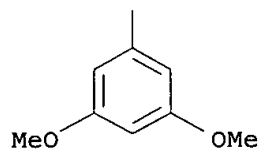
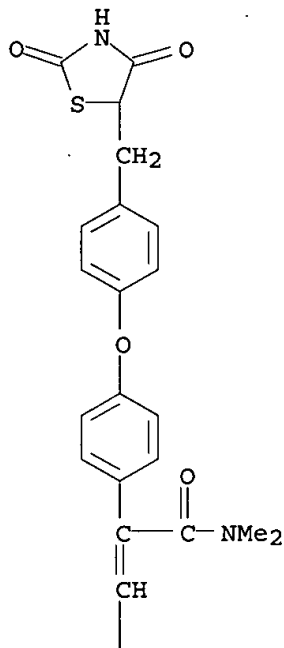


PAGE 2-A



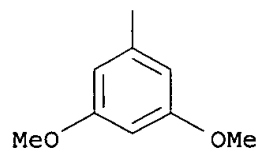
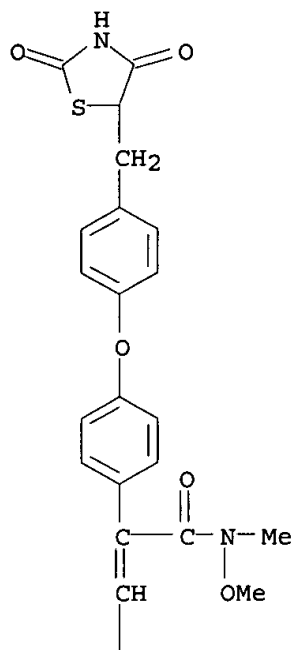
RN 380881-39-0 CAPLUS  
CN Benzeneacetamide, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]-N,N-dimethyl- (9CI) (CA INDEX NAME)





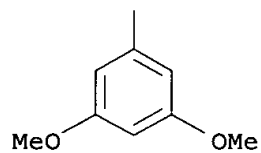
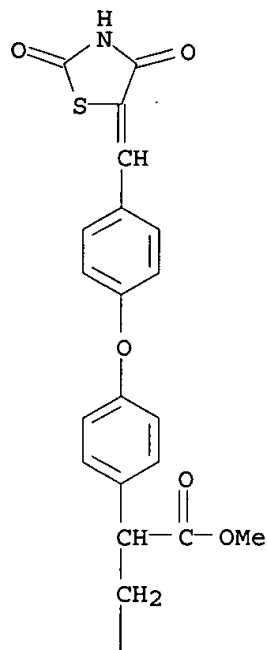
RN 380881-41-4 CAPLUS  
 CN Benzeneacetamide, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]-N-methoxy-N-methyl- (9CI) (CA INDEX NAME)





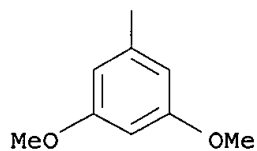
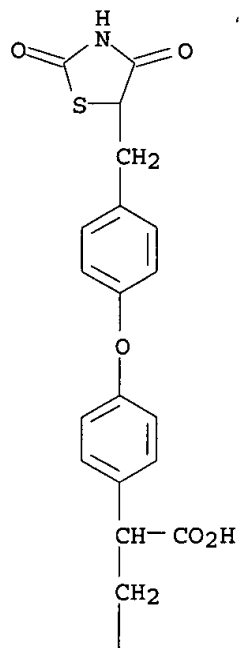
RN 380881-47-0 CAPLUS  
 CN Benzenepropanoic acid, .alpha.-[4-[4-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenoxy]phenyl]-3,5-dimethoxy-, methyl ester  
 (9CI) (CA INDEX NAME)





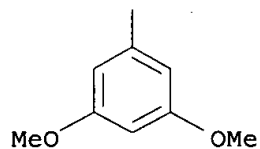
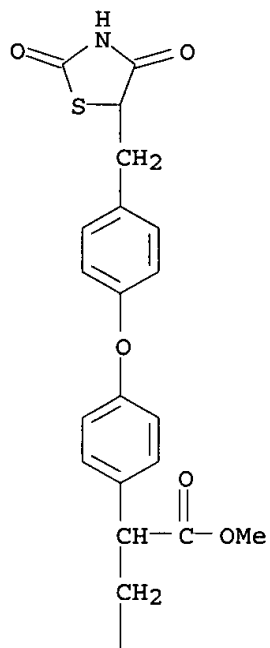
RN 380881-49-2 CAPLUS  
 CN Benzenepropanoic acid, .alpha.-[4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]phenyl]-3,5-dimethoxy- (9CI) (CA INDEX NAME)





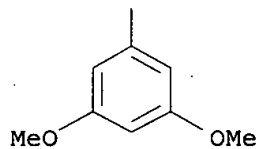
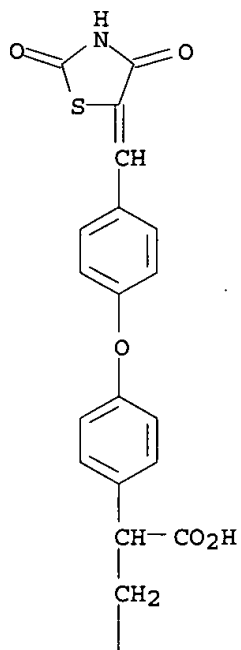
RN 380881-51-6 CAPLUS  
 CN Benzenepropanoic acid, .alpha.-[4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]phenyl]-3,5-dimethoxy-, methyl ester (9CI)  
 (CA INDEX NAME)





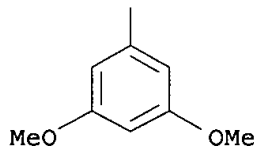
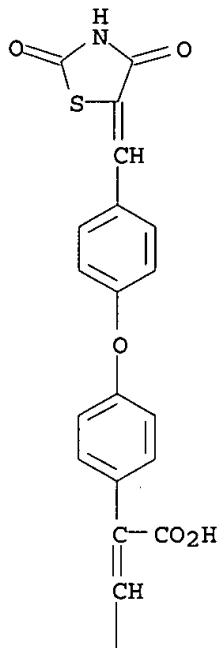
RN 380881-53-8 CAPLUS  
CN Benzenepropanoic acid, .alpha.-[4-[4-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenoxy]phenyl]-3,5-dimethoxy- (9CI) (CA INDEX NAME)





RN 380881-55-0 CAPLUS  
 CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenoxy]- (9CI) (CA INDEX NAME)





L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS  
 AN 1999:736478 CAPLUS  
 DN 131:332116  
 TI Heterocyclic analogs of diphenylethylene compounds for the treatment of diabetes  
 IN Neogi, Partha; Nag, Bishwajit; Medicherla, Satyanarayana; Dey, Debendranath  
 PA Calyx Therapeutics, Inc., USA  
 SO PCT Int. Appl., 34 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 5

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9958127	A1	19991118	WO 1999-US9982	19990507
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,				



09/584,952

CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6245814	B1	20010612	US 1998-74925	19980508
AU 9939741	A1	19991129	AU 1999-39741	19990507
AU 751235	B2	20020808		
EP 1007039	A1	20000614	EP 1999-922836	19990507

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

JP 2002514598	T2	20020521	JP 2000-547978	19990507
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PRAI US 1998-74925 A 19980508  
US 1999-287237 A 19990406  
WO 1999-US9982 W 19990507

OS MARPAT 131:332116

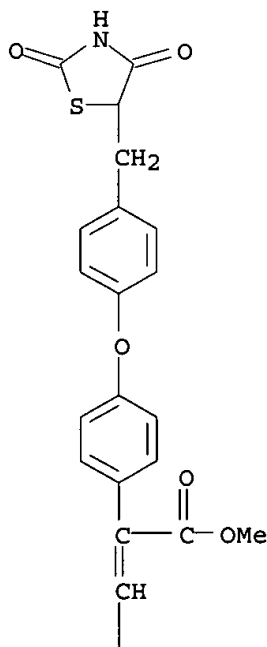
AB Diphenylethylene compds. contg. thiazolidinedione or oxazolidinedione moieties are provided which are effective in lowering blood glucose level, serum insulin, triglyceride and free fatty acid levels in animal models of Type II diabetes. In contrast to previously reported thiazolidine compds., known to lower leptin levels, the present compds. increase leptin levels and have no known liver toxicity.

IT 249886-47-3  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(heterocyclic analogs of diphenylethylene compds. for treatment of diabetes)

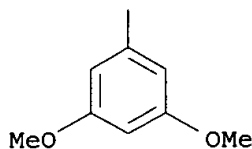
RN 249886-47-3 CAPLUS

CN Benzeneacetic acid, .alpha.-[(3,5-dimethoxyphenyl)methylene]-4-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]-, methyl ester (9CI) (CA INDEX NAME)

PAGE 1-A







RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS  
AN 1996:537366 CAPLUS  
DN 125:195674  
TI Preparation of 2,4-dioxo-1,2,3,4-tetrahydroquinazoline derivatives having  
blood sugar-lowering and aldose reductase-inhibiting activity  
IN Myaoka, Shozo; Sato, Hiroko; Matsushima, Hiroaki; Sugizaki, Myoshi  
PA Terumo Corp, Japan  
SO Jpn. Kokai Tokkyo Koho, 33 pp.  
CODEN: JKXXAF  
DT Patent  
LA Japanese  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 08143566	A2	19960604	JP 1994-291053	19941125
PRAI	JP 1994-291053		19941125		
OS	MARPAT 125:195674				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The title compds. [I; R3, R4 = H, halo, lower alkyl, lower alkoxy, haloalkyl; R1, R2 = R5-CO2R6, CH2C6H4-A-T, (CH2)m-B-T; wherein R5 = C1-3 alkylene; R6 = H, C1-8 alkyl; A = CH2, 1,2-, 1,3-, or 1,4-NHSO2C6H4CH2, -CH2CH2C6H4CH2, or -CH:CHC6H4CH2; T = heterocyclyl having weakly acidic H; m = 1-7; B = NHSO2-C6H4-CH2], which are useful for the treatment of diabetes complications such as cataract, retinopathy, or nerve or kidney disorders, are prepd. Thus, Et 2,4-dioxo-2H-3,1-benzoxazine-1(4H)-acetate, 4-nitrobenzyl amine hydrochloride, and Et3N were suspended in toluene and stirred at 100.degree. for 2.5 h to give Et [2-[N-(4-nitrobenzyl)carbamoyl]phenylamino]acetate, which was cyclocondensed with 1,1'-carbonyldiimidazole at 130.degree. for 2 h to I (R1 = 4-nitrobenzyl, R2 = CH2CO2Et, R3 = R4 = H), diazotized with NaNO2 in HBr/aq. acetone at 5.degree., and coupled with Et acrylate in the presence of Cu2O at 30.degree. to give I (R1 = Q, R2 = CH2CO2Et, R3 = R4 = H). The latter compd. was cyclocondensed with thiourea in the presence of AcONa in ethanol under reflux for 6 h to I (R1 = Q1, wherein Z = NH, R2 = CH2CO2Et, R3 = R4 = H), which was hydrolyzed in 2 N aq. HCl under reflux to give I (R1 = Q1, wherein Z = O, R2 = CH2CO2Et, R3 = R4 = H) and I (R1 = Q1, wherein Z = O, R2 = CH2CO2H, R3 = R4 = H). I (R1 = Q2, R2 = CH2CO2H, R3 = 7-Cl, R4 = H) and I (R1 = Q3, R2 = CH2CO2H, R3 = R4 = H) in vitro showed IC50 of 3.34 .times. 10-8 and 2.13 .times. 10-6 M, resp., against aldose reductase, and at 100 mg/kg/day p.o. for 2 days in vivo lowered blood sugar by 13 and 36%, resp.

IT 180632-29-5P 180632-30-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

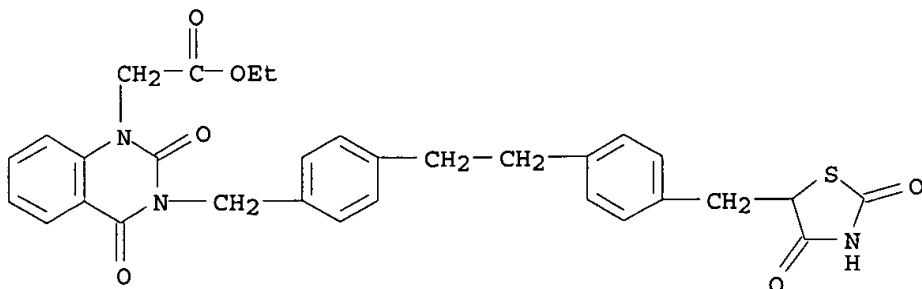


09/584,952

(prepn. of dioxotetrahydroquinazoline derivs. having blood sugar-lowering and aldose reductase-inhibiting activity for treating diabetes complications)

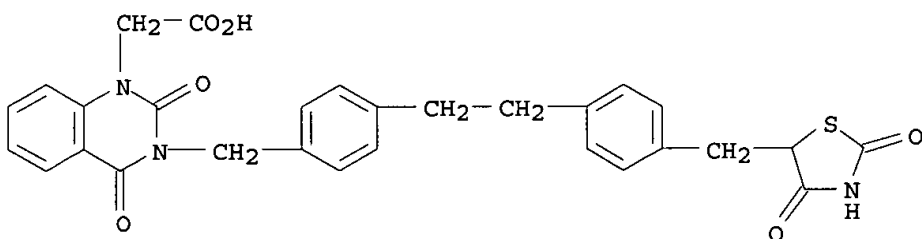
RN 180632-29-5 CAPLUS

CN 1(2H)-Quinazolineacetic acid, 3-[[4-[2-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenyl]ethyl]phenyl]methyl]-3,4-dihydro-2,4-dioxo-, ethyl ester (9CI) (CA INDEX NAME)



RN 180632-30-8 CAPLUS

CN 1(2H)-Quinazolineacetic acid, 3-[[4-[2-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenyl]ethyl]phenyl]methyl]-3,4-dihydro-2,4-dioxo-, (9CI) (CA INDEX NAME)



L4 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS

AN 1992:255519 CAPLUS

DN 116:255519

TI Novel thiazolidine-2,4-diones as potent euglycemic agents.

AU Hulin, Bernard; Clark, David A.; Goldstein, Steven W.; McDermott, Ruth E.; Dambek, Paul J.; Kappeler, Werner H.; Lamphere, Charles H.; Lewis, Diana M.; Rizzi, James P.

CS Pfizer Inc., Groton, CT, 06340, USA

SO Journal of Medicinal Chemistry (1992), 35(10), 1853-64

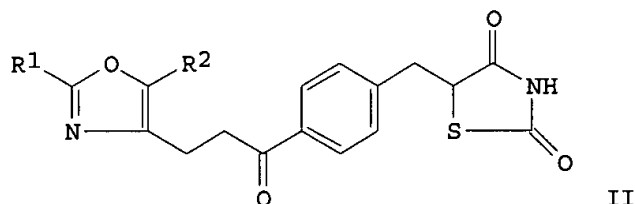
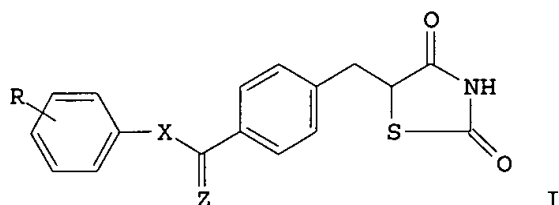
CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

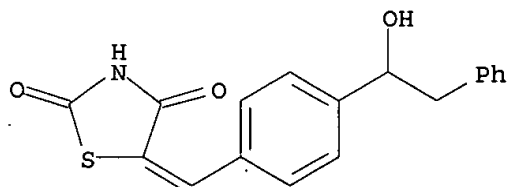
LA English

GI





- AB A new series of thiazolidine-2,4-diones I [R = H, Z = O, X = (CH<sub>2</sub>)<sub>n</sub>, (n = 1, 2, 3), OCH<sub>2</sub>, CH:CH; R = 4-PhCH<sub>2</sub>O, 4-Ph, 2-MeO, 4-MeO, Z = O, X = CH<sub>2</sub>CH<sub>2</sub>; R = H, Z = H<sub>2</sub> or H,OH, X = CH<sub>2</sub>CH<sub>2</sub>; R = 4-PhCH<sub>2</sub>O, 2-MeO, 2-Cl, 2-CF<sub>3</sub>, 2-PhCH<sub>2</sub>, 3-Cl, 4-Br, 4-EtO<sub>2</sub>C, 4-Ph, 2-HO, 2-Me, 4-MeOCH<sub>2</sub>, 4-MeO, 4-Me<sub>2</sub>N, Z = O, X = CH:CH] was obtained by replacing the ether function of englitazone with various functional groups, i.e., a ketone, alc., or olefin moiety. These compds. lower blood glucose levels in the genetically obese and insulin-resistant ob/ob mouse. Appending an oxazole-based group at the terminus of the chain provided highly potent compds., e.g. II [R<sub>1</sub> = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = Me, H; R<sub>1</sub> = 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-HOC<sub>6</sub>H<sub>4</sub>, 3,5,4-Me<sub>2</sub>(MeO)C<sub>6</sub>H<sub>2</sub>, 3,5,4-Me<sub>2</sub>(HO)C<sub>6</sub>H<sub>2</sub>, 2-furyl, 2-(5-methylfuryl), 2-HSC<sub>6</sub>H<sub>4</sub>, 2-naphthyl, R<sub>2</sub> = Me].
- IT **141200-90-0P**  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. and condensation of, with thiazolidinedione)
- RN 141200-90-0 CAPLUS
- CN 2,4-Thiazolidinedione, 5-[[4-(1-hydroxy-2-phenylethyl)phenyl]methylene]-  
 (9CI) (CA INDEX NAME)

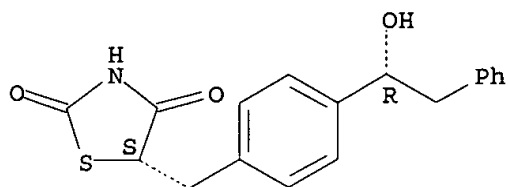


- IT **141200-92-2P**  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (prepn. and conjugate redn of, in prepn. of euglycemics)
- RN 141200-92-2 CAPLUS
- CN 2,4-Thiazolidinedione, 5-[[4-(1-hydroxy-2-phenylethyl)phenyl]methyl]-,  
 (R\*,S\*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



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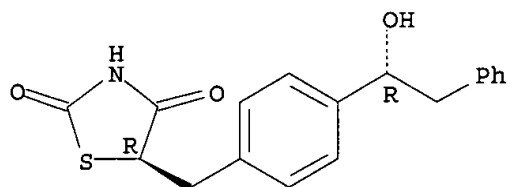
IT 141200-91-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(prepn. and conjugate redn. of, in prepn. of euglycemics)

RN 141200-91-1 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-(1-hydroxy-2-phenylethyl)phenyl]methyl]-,  
(R\*,R\*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

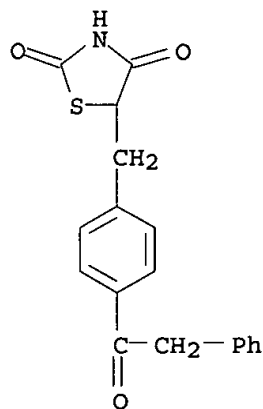


IT 141199-89-5P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. and euglycemic activity of)

RN 141199-89-5 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-(phenylacetyl)phenyl]methyl]- (9CI) (CA  
INDEX NAME)



=>